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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/683,815      | 10/09/2003  | Arnon Rosenthal      | 514712001500        | 5142             |

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| EXAMINER |
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BALLARD, KIMBERLY A

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| ART UNIT | PAPER NUMBER |
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1649

DATE MAILED: 07/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/683,815             | ROSENTHAL ET AL.    |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Kimberly A. Ballard    | 1649                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-54 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-54 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                                    |                                                                             |
|----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____                                                |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>05/03/06</u> .                                                            | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Response to Amendment***

1. Applicant's response and amendments to claims submitted 03 May 2006 have been entered. Applicant has amended claims 1, 10, 13, 22, 26, 35, 39, and 48 and has added new claims 51-54. Accordingly, claims **1-54** are pending and under consideration in the instant office action.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

### ***Information Disclosure Statement***

4. A signed and initialed copy of the IDS paper submitted 03 May 2006 is enclosed in this action. The IDS papers submitted 30 August 2004 and 27 September 2005 have previously been considered and entered of record.

### ***Withdrawn Objections and Claim Rejections***

5. The objection to claims 8, 9, 20, 21, 33, 34, 46 and 47 as set forth at p. 2 of the previous office action mailed 31 January 2006 is hereby withdrawn in view of Applicant's amendment to the sequence listing.

6. The objection to claims 1-50 as set forth at p. 2 of the previous office action mailed (01/31/2006) is hereby withdrawn in view of Applicant's amendments to the claims.

***Maintained Claim Rejections***

***35 USC § 112, 1<sup>st</sup> paragraph***

7. The rejection of claims 39-50 under 35 USC § 112, first paragraph, as set forth at pp. 3-6 of the 01/31/2006 office action is maintained for reasons of record set forth in the office action dated 01/31/2006. Further, new claim 54 is also rejected under 35 USC § 112, first paragraph, for reasons of record and for reasons stated below.

In the response filed 05/03/2006, Applicants argue that the instant application teaches how to make and use the claimed invention. Without acquiescence to the rejection, Applicants have amended claim 39 to recite "delaying development of a symptom associated with Alzheimer's disease in a subject having Alzheimer's disease."

Applicants' arguments and claim amendments have been fully considered but are not found to be persuasive. While the amendment to claim 39 does address some of the issues set forth in the rejection, it does not overcome the rejection. The claims

Art Unit: 1649

still encompass delaying development of any symptom associated with Alzheimer's disease in a subject with Alzheimer's disease, however, the instant specification teaches only a reduction in brain pathology (i.e., reduced amyloid deposits and thioflavine-S positive compact plaques) in transgenic Tg2576 mice administered anti-A $\beta$  antibodies. The brains of Tg2576 mice injected peripherally or intracranially with monoclonal anti-A $\beta$  antibodies were evaluated histopathologically 3 days following treatment. A treatment effect examined at only at a single time point does not enable the breadth of a delayed development of symptoms despite the fact that a reduction in amyloid burden was noted in these animals. As noted previously, as the age of Tg2576 mice increases so do behavioral deficits and elevated brain A $\beta$  levels. However, no examples of the effects of anti-A $\beta$  antibodies on delaying the development of these symptoms are provided, such as an evaluation of treatment effect on disease progression (e.g. amyloid plaque burden) examined over the course of weeks or months in comparison to control Tg2576 mice of the same age. Moreover, no examples, prophetic or otherwise, of symptoms other than amyloid-associated pathology in the brain or circulation are provided. The instant specification hence teaches reduction of amyloid brain pathology in transgenic mice, but insufficient guidance is provided for delaying the development of symptoms associated with Alzheimer's disease as broadly claimed. Thus, the model system used in the instant specification is not recognized as providing for teachings that are predictive of the results that would be expected for the full scope of the claims. For example, the art recognizes that such *in vivo* models are not readily correlated to the human *in vivo* case. In particular, the art teaches a lack of

correlation of beneficial effects shown in the mouse model system in humans; see in particular Münch & Robinson (July 2002, "Potential Neurotoxic Inflammatory Responses to A $\beta$  Vaccination in Humans." *J. Neural Transmission*, 109(7-8): 1081-1087).

Due to the large quantity of experimentation necessary to determine the effectiveness of delaying development of Alzheimer's disease symptoms in subjects with Alzheimer's disease, the lack of direction/guidance presented in the specification regarding the same, the complex nature of the invention, the state of the prior art with respect to such treatment, the unpredictability of therapy as evidenced in the art, and the breath of the claims which effectively fail to limit a specific symptom, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

#### ***Obviousness-Type Double Patenting***

8. The provisional rejection of instant claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 over claims 1, 4, 7-17, 19, 28, 31-40 and 42 of copending Application No. 11/194,989 is maintained for reasons of record set forth in the office action dated 01/31/2006 and held in abeyance until all other rejections are resolved. Further, new claims 51-54 are also rejected over claims 2 and 30 of the '989 application for reasons of record in said office action.

9. The provisional rejection of instant claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 over claims 1, 3, 6-15, 17, 26, 29-38 and 40 of copending

Art Unit: 1649

Application No. 11/195,207 is maintained for reasons of record set forth in the office action dated 01/31/2006 and held in abeyance until all other rejections are resolved. Further, new claims 51-54 are also rejected over claims 2 and 28 of the '207 application for reasons of record in said office action.

**35 USC § 102**

10. The rejection of claims 1, 2, 4, 6, 8-10, 13, 14, 16, 18, 20-22, 25-27, 29, 31, 33-35, 38-40, 42, 44, and 46-48 under 35 U.S.C. 102(b) as being unpatentable over Bard et al. (*Nat Med*, August 2000; 6(8): 916-919) as set forth at pp. 9-11 of the previous office action mailed 01/31/2006 is maintained for reasons of record in the previous office action.

In the response filed 05/03/2006, Applicants argue that Bard et al. do not teach or suggest the claimed invention. Applicants submit the disclosure in Bard et al. cannot be said to be an enabling reference for teaching the use of an antibody as claimed for treating Alzheimer's disease. Applicants further submit that the 21F12 antibody, with a noted epitope of A $\beta$ <sub>33-42</sub>, used by Bard et al. "does not necessarily suggest that this antibody preferentially binds to amino acids 28-40 of A $\beta$ <sub>1-40</sub>."

Applicants' arguments have been fully considered but are not found to be persuasive. The instant specification defines that an antibody "preferentially binds" (or "specifically binds", used interchangeably) "to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration that it binds to other substances." The specification goes on to state that as such, ""preferential binding" does not necessarily

require...exclusive binding" (paragraph [0055]). The claims are broadly drawn to methods of treating Alzheimer's disease comprising administering to the subject an effective amount of an antibody that *preferentially* binds to amino acids 28-40 of A $\beta$ <sub>1-40</sub> and a pharmaceutically acceptable carrier. Using a transgenic mouse model of Alzheimer's disease similar to what was used in the instant specification, Bard evaluates antibodies for therapeutic use in the treatment of Alzheimer's disease and other neurological disorders. One such antibody taught by Bard is the monoclonal antibody 21F12, which has a reported epitope of A $\beta$ <sub>33-42</sub> and a reported affinity for soluble A $\beta$  (A $\beta$ <sub>1-40</sub> is the soluble form of A $\beta$ ) of 80 nM (see Table 1, p. 918). The 21F12 monoclonal antibody taught by Bard et al. would therefore meet the limitations of *preferentially* binding to amino acids 28-40 of A $\beta$ <sub>1-40</sub> as the epitope for 21F12 comprises A $\beta$ <sub>33-40</sub>, and also of having an affinity for A $\beta$ <sub>1-40</sub> of about 200 nM or less. Moreover, because of the definition of "preferential binding" presented in the instant specification, the antibody of Bard et al. also meets the limitation of not having significant cross-reactivity with A $\beta$ <sub>1-42</sub> and A $\beta$ <sub>1-43</sub> peptides. Further, there is nothing in the reference or other prior art to suggest that the 21F12 monoclonal antibody would not preferentially bind to an epitope that includes amino acid 39 and/or 40 of A $\beta$ <sub>1-40</sub> because these residues are also encompassed within the 21F12 epitope. The antibody 21F12 was administered in a pharmaceutically acceptable carrier to a subject (PDAPP mice) with the intention of treatment of Alzheimer's disease and/or for reduction amyloid burden in the brains of the subjects. The instant claims are thus anticipated by the Bard et al. reference because a reference need not have described an actual reduction to practice

Art Unit: 1649

of an invention in order to serve as an anticipatory reference. See *In re Siveramakrishnan*, 673 F.2d 1383, 1384, 213 USPQ 441, 442 (CCPA 1982); *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985). Moreover, even if a reference does not explicitly set forth every element of the claim, the reference may still be an anticipatory reference if the element is inherent in the disclosure. See *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed Cir 1999). In the instant case the Bard et al. reference explicitly suggests the step of administering an effective amount of a pharmaceutical composition comprising a monoclonal anti-A $\beta$  antibody to a subject for the treatment of Alzheimer disease, wherein the disclosed antibody meets several of the claim limitations.

Accordingly, the claims as written still read upon the treatment method using the 21F12 antibody taught by Bard, and by the principle of inherency, the 21F12 antibodies would thus reasonably be expected to perform the same as the claimed invention. Thus, Bard anticipates the instant claims.

11. The rejection of claims 1, 2, 8-14, 20-27, 33-40, and 46-50 under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,787,523 B1 to Schenk, September 7, 2004, filed November 30, 1998, as set forth at pp. 11-14 of the previous office action mailed 01/31/2006 is maintained for reasons of record in the previous office action. Further, new claims 51-54 are similarly rejected for reasons of record and for reasons stated below.

In the response filed 05/03/2006, Applicants argue that the disclosures in Schenk do not teach or suggest the claimed invention. Applicants submit the disclosure in Schenk cannot be said to be an enabling reference for teaching the use of an antibody as claimed for treating Alzheimer's disease. For example, Applicants submit that in a related PCT application by Schenk et al. (WO 00/72880), that the antibody 21F12 "did not show significant treatment effects in the animal model" and that the combined disclosures of WO 00/72880 and Bard et al. (as above) suggest that antibodies directed to epitopes within residues 33-42 lack activity. Finally, Applicants assert that the 21F12 antibody may not necessarily meet the binding specificities recited in the claims.

Applicants' arguments have been fully considered but are not found to be persuasive. As discussed above, the 21F12 monoclonal antibody taught by Schenk meets the limitations of *preferentially* binding to amino acids 28-40 of A $\beta$ <sub>1-40</sub> as the epitope for 21F12 comprises A $\beta$ <sub>33-40</sub>, and also of having an affinity for A $\beta$ <sub>1-40</sub> of about 200 nM or less (as taught by Bard et al.) Further, there is nothing in the reference or other prior art to suggest that the 21F12 monoclonal antibody would not *preferentially* bind to an epitope that includes amino acid 39 and/or 40 of A $\beta$ <sub>1-40</sub> because these residues are also encompassed within the 21F12 epitope. And, as noted in the Applicants' disclosure, binding *preferentially* does not necessarily require exclusive binding.

Applicants are claiming a method of treating Alzheimer's disease in a subject by administering an effective amount of an antibody that *preferentially* binds to amino acids 28-40 of A $\beta$ <sub>1-40</sub> and a pharmaceutically acceptable carrier. Claimed characteristics of

the antibody include that it binds preferentially to an epitope that includes amino acid 39 and/or 40 of the A $\beta$ <sub>1-40</sub> peptide, it competitively inhibits binding of a monoclonal antibody to A $\beta$ <sub>1-40</sub>, it is a monoclonal antibody, it is a humanized antibody, or it is a human antibody. The population of subjects being administered the antibody are those subjects, in particular transgenic mice, which have Alzheimer's disease-related pathology, or they are human patients. As noted above and in the previous office action, the disclosure by Schenk of the 21F12 antibody meets all the recited antibody claim limitations. Hence, the method of administering to a subject such an antibody meeting all the recited limitations would reasonably be expected to achieve the desired objective of treatment of Alzheimer's disease and/or reduction of amyloid pathology. Accordingly, the claims as written still read upon the method of treating Alzheimer's disease using the 21F12 antibody taught by Schenk, and under the principle of inherency, the 21F12 antibody would thus reasonably be expected to perform the same as the claimed invention. It is further noted that because Schenk et al. fully anticipate the claimed methods, the instantly claimed invention would also be subject to any alleged deficiencies related to the enablement of the antibodies noted in the prior art.

**35 USC § 103**

12. The rejection of claims 1, 2, 4-14, 16-27, 29-40, and 42-50 under 35 U.S.C. 103(a) as being unpatentable over Bard et al. (*Nat Med*, August 2000, 6(8): 916-919, cited on Applicant's IDS received 8/30/04) in view of Zeitlin et al. (*Microbes and Infection*, 2000, 2: 701-708) as set forth at pp. 14-16 of the previous office action mailed

01/31/2006 is maintained for reasons of record in the previous office action. Further, new claims 51-54 are similarly rejected for reasons of record and for reasons stated below.

In the response filed 05/03/2006, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants argue that the cited references, even if combined, do not teach or suggest all of the claimed limitations, wherein Bard et al. does not teach or suggest methods for treating Alzheimer's disease by administering an antibody that binds preferentially to amino acids 28-40 of A $\beta$ <sub>1-40</sub> peptide, and Zeitlin et al. do not teach or suggest using an anti-A $\beta$  antibody for treating Alzheimer's disease. Applicants therefore submit that it would not have been obvious to combine the teachings of these two references with a reasonable expectation of success in removing plaques and treating Alzheimer's disease. Further, Applicants argue that Bard et al. teach away from the concept of using antibodies directed to C-terminal amino acid residues of an A $\beta$  peptide to clear amyloid plaques, and thus one skilled in the art would not have been motivated to make and use these antibodies and have a reasonable expectation of success.

Applicants' arguments have been fully considered but are not found to be persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Bard et al. teach the use of anti-A $\beta$  antibodies, both polyclonal and monoclonal, for reduction of amyloid pathology in brains of transgenic PDAPP mice, and suggest that the disclosed antibodies should be considered as a therapeutic approach for the treatment of Alzheimer disease and other neurological disorders (see reasons of record with respect to Bard et al. reference applied as 102 art *supra*). Zeitlin et al. teach that the protective duration of monoclonal antibodies used therapeutically for the treatment and prevention of specific diseases could be improved if the antibody's affinity were also improved, and further that immunogenicity problems can be effectively reduced or eliminated with the advent of technology enabling the production of humanized or fully human monoclonals, thus allowing monoclonal antibodies to achieve their full potential as clinically useful molecules. It is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Thus, taking together the teachings of Bard et al. and Zeitlin et al, one of skill in the art would be

motivated to develop practical therapeutic approaches for the treatment of the Alzheimer's disease in humans such as therapies that have a longer duration of action (i.e., high affinity monoclonal antibodies requiring fewer therapeutic administrations) and are better tolerated by the patient (i.e., humanized or human antibodies which are less immunogenic).

Therefore, in view of the above teachings and those of record in the previous office action, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to practice the instant claimed method as disclosed by Bard et al. by administering a high-affinity monoclonal, humanized antibody or human antibody to a patient. The motivation to combine the teachings of the above references and a reasonable expectation of success have been addressed *supra* and in previous the office action. Thus, the combined references render obvious claims 1, 2, 4-14, 16-27, 29-40, and 42-54.

### ***Conclusion***

13. No claims are allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

Art Unit: 1649

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.  
Art Unit 1649  
July 11, 2006

  
OLGA N. CHERNYSHEV, PH.D.  
PRIMARY EXAMINER